Electronic Supplementary Material (ESI) for Green Chemistry.

Increasing Global Access to the High-Volume HIV Drug Nevirapine through Process Intensification

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Supporting Information

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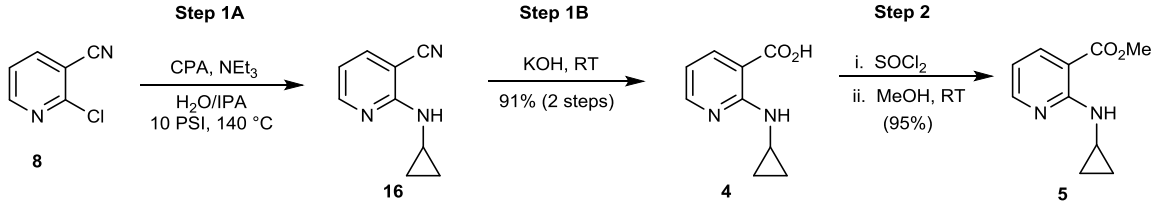
General Information

All commercially available reagents were purchased from Acros Organics, Sigma-Aldrich, TCI or Alfa Aesar and used as received. Reaction temperatures were monitored using a J-KEM temperature controllers and thermocouples. Thin layered chromatography (TLC) was performed using silica gel 60 F254 plates. Proton nuclear magnetic resonance (1 H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a Varian Mercury-300 MHz. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane. Chemical shifts for carbon are reported in parts per million (ppm) downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration. HPLC chromatographs were acquired either on an Agilent 1260 Infinity system using an Agilent Poroshell 120 EC-C18 column (2.7 µm, 4.6 mm x 50 mm) applying a gradient of 5% ACN in H_2O to 95% ACN in H_2O from 0.5 min to 6.5 min at a flow rate of 1.5 mL/min or on a Waters Acuity UPLC H-Class system using a Waters BEH C18 column (1.7 µm, 2.1 mm x 50 mm) applying a gradient of 5% ACN in H_2O to 90% ACN in H_2O from 0.5 min to 9.0 min at a flow rate of 0.6 mL/min, followed by a hold at 90% ACN from 9.0 min to 10.0 min. High resolution mass spectra were obtained through the Virginia Commonwealth University Chemical and Proteomic Mass Spectrometry Core Facility using a Orbitrap Velos mass spectrometer from Thermo Electron Corporation.

Experimental Procedures

Preparation of MeCAN (5)



MeCAN Step 1A: To a 250 mL pressure vessel was sequentially added 2-chloro nicotinonitrile (**8**) (20.0 g, 144.35 mmol, 1.0 equiv), cyclopropylamine (10 ml, 144.35 mmol, 1.0 eq.), triethylamine (20.11 ml, 144.35 mmol, 1.0 eq.), water (60 ml) and IPA (80 mL) were added. The vessel was pressurized to 10 psi with N_2 gas and the reaction mixture was heated to 140 °C to reach a final pressure of 60 psi. After 6 hours at 140 °C, the reaction mixture was cooled to RT, depressurized and used directly in the next step. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.32 (dd, *J* = 2.0, 4.9 Hz, 1 H), 7.88 (dd, *J* = 2.0, 7.6 Hz, 1 H), 7.33 - 7.18 (m, 1 H), 6.69 (dd, *J* = 4.9, 7.8 Hz, 1 H), 2.77 (dt, *J* = 3.2, 7.0 Hz, 1 H), 0.71 - 0.65 (m, 2 H), 0.60 - 0.55 (m, 2 H). ^{13}C NMR (75MHz, DMSO-d_6) δ = 159.1, 152.8, 142.6, 116.9, 112.1, 90.3, 24.4, 6.8. HRMS (ESI) $C_9H_9N_3$ *m/z* $[M+H]^+$ found 160.0853, expected 160.0875.

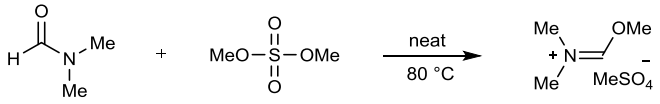
MeCAN Step 1B: To a 3-neck flask fitted was added the crude reaction mixture from step 1A followed by solid KOH pellets (24.29 g, 433.05 mmol, 3.0 equiv). An exotherm

from room temperature to 40°C was observed. The reaction mixture was stirred at reflux. After 12 hours, the mixture was cooled to 0 °C and con. HCl (42.7 ml, 433.05 mmol, 3.0 equiv) was charged drop-wise to bring the pH of the mixture to 6 while maintaining a temperature below 10 °C. A white solid precipitate was collected via vacuum filtration. The wet cake was washed with a minimal amount of water and dried at 75 °C in vacuo to a constant weight (23.40 g, 91%). ^{1}H NMR (DMSO-d_6, 600MHz): δ = 8.29 (dd, *J*=4.7, 1.8 Hz, 1 H), 8.05 (dd, *J*=7.6, 2.3 Hz, 1 H), 6.63 (dd, *J*=7.6, 5.3 Hz, 1 H), 2.80 - 2.88 (m, 1 H), 0.70 - 0.77 (m, 2 H), 0.43 - 0.49 ppm (m, 2 H). ^{13}C NMR (DMSO-d_6, 151MHz): δ = 168.9, 159.2, 153.1, 139.9, 111.7, 106.4, 23.7, 6.9 ppm. HRMS (ESI) $C_9H_{10}N_2O_2$ *m/z* $[M+H]^+$ found 179.0797, expected 179.0820.

MeCAN Step 2: To a suspension of 2-CAN (**4**, 30g, 53.45 mmole. 1 equiv.) in toluene (150 ml) in a 250 mL, 3-neck flask fitted with thermocouple and stirrer under N_2, was added thionyl chloride (50.5 ml, 69.48 mmole, 1.3 equiv) at room temperature over five minutes. An exotherm to 40-50 °C was observed and the mixture was stirred for 30 minutes. Methanol (34 mL) was added dropwise over 10 minutes while maintaining the reaction mixture temperature below 50°C. After stirring for 2 hours, the reaction mixture cooled to room temperature and the excess methanol was removed in vacuo.

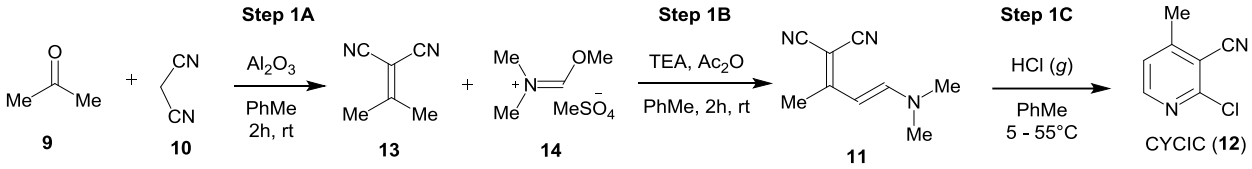
After cooling the reaction mixture to 0 °C, H_2O (100 mL) was added and the pH was adjusted with a 20% solution of NaOH to pH ~ 9. The aqueous phase was extracted with toluene (2 x 25 mL) and the combined organic layers were washed with water (25ml), dried with Mg_2SO_4, filtered, and concentrated in vacuo to produce MeCAN as an oil (30.75g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (dd, *J* = 2.01, 4.77 Hz, 1H), 8.11 (dd, *J* = 2.01, 7.78 Hz, 1H), 8.06 (br. s., 1H), 6.58 (dd, *J* = 4.89, 7.65 Hz, 1H), 3.86 (s, 3H), 2.92 (dt, *J* = 3.39, 6.96 Hz, 1H), 0.82 - 0.94 (m, 2H), 0.51 - 0.61 (m, 2H). ^{13}C NMR (101MHz, $CDCl_3$) δ = 167.8, 159.6, 153.7, 139.7, 111.4, 106.1, 51.8, 23.7, 7.1. HRMS (ESI) $C_{10}H_{12}N_2O_2$ *m/z* $[M+H]^+$ found 193.0965, expected 193.0977.

Preparation of DMF-DMS adduct (14)



To a 3-neck 1-L round bottom flask was added dimethyl-formamide (77.4 ml, 1.0 mole, 1.0 equiv) and dimethyl sulfate (94.8 ml, 1.0 mole, 1.0 equiv) under N_2. The reaction mixture was stirred at room temperature for 5-10 minutes, stirred at 60 °C for 30 minutes then slowly heated to 70–80°C and stirred for 4–6 hours. The reaction was then cooled to room temperature. The yield was quantitative and purity was >95%. The reagent was used in the subsequent step without further purification. ^{1}H NMR (300MHz, DMSO-d^6, ppm) δ 8.69 (s, 1H), 4.28 (s, 3H), 3.40 (s, 3H), 3.31 (s, 3H), 3.11 (s, 3H). Spectra in accordance with those described in the literature.[1]

Preparation of 2-chloro-4-methylnicotinonitrile (CYCIC, 12)



CYCIC Step 1A: To a 1-L 3-neck round-bottom flask fitted with an overhead stirrer and thermocouple was added aluminum oxide (activated basic, Brockman, 58Å pore size) (183 g, 1.8 mole, 1.2 equiv) followed by malononitrile (100 g, 1.51 mole, 1.0 equiv) and toluene (600 mL). The reaction mixture was stirred at 15–20°C until dissolution of malononitrile was observed. To the reaction mixture was added acetone (111 mL, 1.51 mole, 1.0 equiv), maintaining a temperature between 15–20 °C. After stirring for 2 hours at room temperature, the reaction mixture was filtered and the aluminium oxide was rinsed with toluene (2 x 25 mL). The filtrate is used directly in the next step 1B. The alkylidene product can be isolated by concentrating the filtrate in vacuo, then performing a short-path distillation with gentle heating. Spectra were in accordance with those described in the literature.[2]

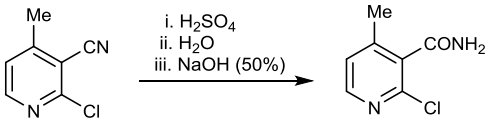
CYCIC Step 1B: To a 100-ml 3-neck flask, fitted with a magnetic stirrer and thermocouple was added sequentially DMF-DMS (49.48 g, 248 mmoles, 1.2 equiv), acetic anhydride (3.91 ml, 41.4 mmoles, 0.2 equiv) and the ylidene stock solution in toluene from step 1A (90 mL, 207 mmoles, 1.0 equiv) under N_2. The biphasic mixture was cooled between 5–10 °C and stirred vigorously. To the reaction mixture was added triethylamine (34.66 ml, 248 mmoles, 1.2 equiv) dropwise while keeping the reaction mixture between 5–15 °C. Precipitation of a bright orange-red solid was observed. After the addition, the reaction mixture was warmed to room temperature and additionally stirred for 2 hours.

If desired, the enamine product can be isolated at this stage by the addition of hexanes (100 mL) to the cooled reaction mixture (0 °C). The resulting oil residue is stirred for about 15 minutes, the hexanes layer is removed and discarded. This step is repeated 4 more times. Water (100 mL) was added to the remaining residue and stir at RT for 10 minutes at which point a precipitate is formed and collected by vacuum filtration. The isolated solid (43.3 g) was dried in vacuo (without heating) to a constant weight of 31.3 g (94%). ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.22 (d, *J* = 12.5 Hz, 1 H), 5.63 (d, *J* = 12.8 Hz, 1 H), 3.21 (s, 3 H), 2.98 (s, 3 H), 2.23 (s, 3 H). ^{13}C NMR (75MHz, $CDCl_3$) δ = 168.1, 152.4, 116.8, 116.0, 96.9, 65.0, 45.7, 37.4, 17.1. HRMS (ESI) $C_9H_{11}N_3$ *m/z* $[M+H]^+$ found 162.1025, expected 162.1031.

CYCIC Step 1C: The reaction mixture from Step 1B was stirred vigorously and cooled to maintain an internal temperature of 20 °C as HCl gas (11.32 g, 310.5 mmoles, 1.5 equiv) was bubbled into the reaction mixture. After complete addition (1-2 hr), the

reaction was heated to 50-55 °C and stirred for 2 hours. The reaction mixture was concentrated in vacuo to remove approximately 75% of the solvent and water was added (150–200 mL) to the residue with stirring. The precipitate is collected by vacuum filtration. The isolated solid (51 g) was dried in vacuo at 30–40 °C to a constant weight of 26.6 g (85%). ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.43 (d, *J* = 5.3 Hz, 1 H), 7.23 (d, *J* = 5.5 Hz, 1 H), 2.61 (s, 3 H). ^{13}C NMR (101MHz, $CDCl_3$) δ = 154.7, 153.2, 151.6, 123.5, 113.8, 111.5, 20.7. HRMS (ESI) $C_7H_5ClN_2$ *m/z* $[M+H]^+$ found 153.0216, expected 153.0219.

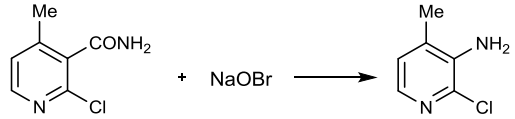
Preparation of COMAD (15).



CYCIC (12) COMAD (15)

To a 250-mL round-bottom flask fitted with a thermocouple and reflux condenser was added CYCIC (**12**) (20.0 g, 131 mmole, 1.0 equiv) followed by sulfuric acid (45.0 g, 459 mmole, 3.5 equiv), controlling rate of addition to maintain a reaction temperature between 40-50°C. The reaction mixture was stirred at 40–50 °C for about 15 minutes until complete dissolution of CYCIC was observed. The mixture was stirred at 105°C for 8 hrs. After cooling to 70-75 °C, water (40 mL) was added to the reaction while maintaining a temperature below 90 °C. Additional water (140 g) was added and the reaction mixture was cooled to 10 °C. A solution of NaOH (50%, 36.7 mL) was added to the reaction mixture while keeping the temperature below 35 °C until the pH reached 11. The resulting suspension was filtered via vacuum filtration and the filter cake was washed with warm water (3 x 20 mL). The isolated solid was dried in vacuo at 30–35 °C to a constant weight of 21.45 g (96%). ^{1}H NMR (400MHz, Acetone-d_6) δ = 8.22 (d, *J* = 5.0 Hz, 1 H), 7.37 (br. s., 1 H), 7.26 (d, *J* = 5.0 Hz, 1 H), 7.08 (br. s., 1 H), 2.80 (s, 1 H), 2.38 (s, 3 H). ^{13}C NMR (101MHz, Acetone-d_6) δ = 167.6, 149.7, 148.2, 147.7, 134.9, 125.4, 19.1. HRMS (ESI) $C_7H_7ClN_2O$ *m/z* $[M+H]^+$ found 171.0320, expected 171.0325.

Preparation of CAPIC (2).

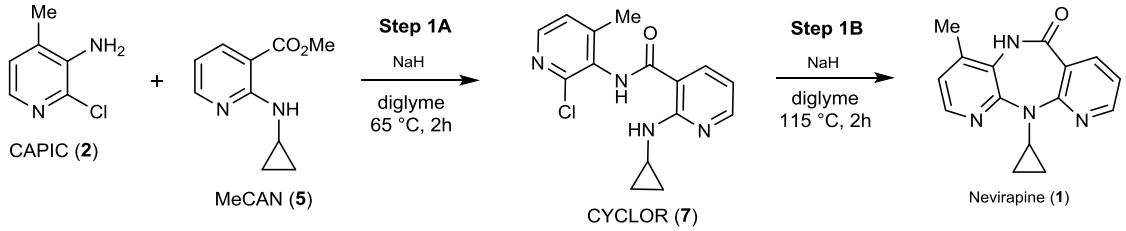


COMAD (15) CAPIC (2)

To a 100 mL, 3-neck flask fitted with thermocouple was added water (25 mL) and a 50% solution of NaOH (19.27g, 482 mmole, 4.0 equiv). The reaction mixture was cooled (0 °C) and Br_2 (10.61 g, 66.4 mmole, 1.1 equiv) was added slowly via addition flask. The reaction mixture was stirred for 30 minutes at 0 °C.

To a separate 250 mL, 3-neck flask fitted with thermocouple, dropping funnel and cooling system was added COMAD (10.3 g, 60.4 mmole, 1.0 equiv) and water (15 mL). To the cooled (0 °C) suspension was added the NaOBr solution and the reaction mixture was stirred for 20 mins as a clear yellow solution was observed. The reaction mixture was allowed to warm to RT and stirred for 1.5 hours. Water (10 mL) was added then the reaction was stirred at 80 °C for 1 hour. After the reaction mixture was cooled to 50 °C, toluene (25 mL) was added and the biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted with toluene (2 x 15 mL). The combined organic layers were washed with water (2 x 15 mL), and concentrated in vacuo to remove about 70% of the solvent. The addition of hexanes (10 mL) with slow agitation induces the precipitation of a white solid. The suspension was kept at 0 °C for about 1 hour. The resulting suspension was collected via vacuum filtration and the filter cake was rinsed with chilled hexanes (10 mL). The isolated solid was dried in vacuo to furnish an off-white to white solid (8.34 g, 97%). ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.71 (d, *J* = 4.8 Hz, 1 H), 6.93 (d, *J* = 4.8 Hz, 1 H), 3.99 (br. s., 2 H), 2.21 (s, 3 H). ^{13}C NMR (101MHz, $CDCl_3$) δ = 138.1, 138.0, 136.7, 131.8, 124.7, 17.3. HRMS (ESI) $C_6H_7ClN_2$ *m/z* $[M+H]^+$ found 143.0370, expected 143.0376.

Preparation of Nevirapine (1).

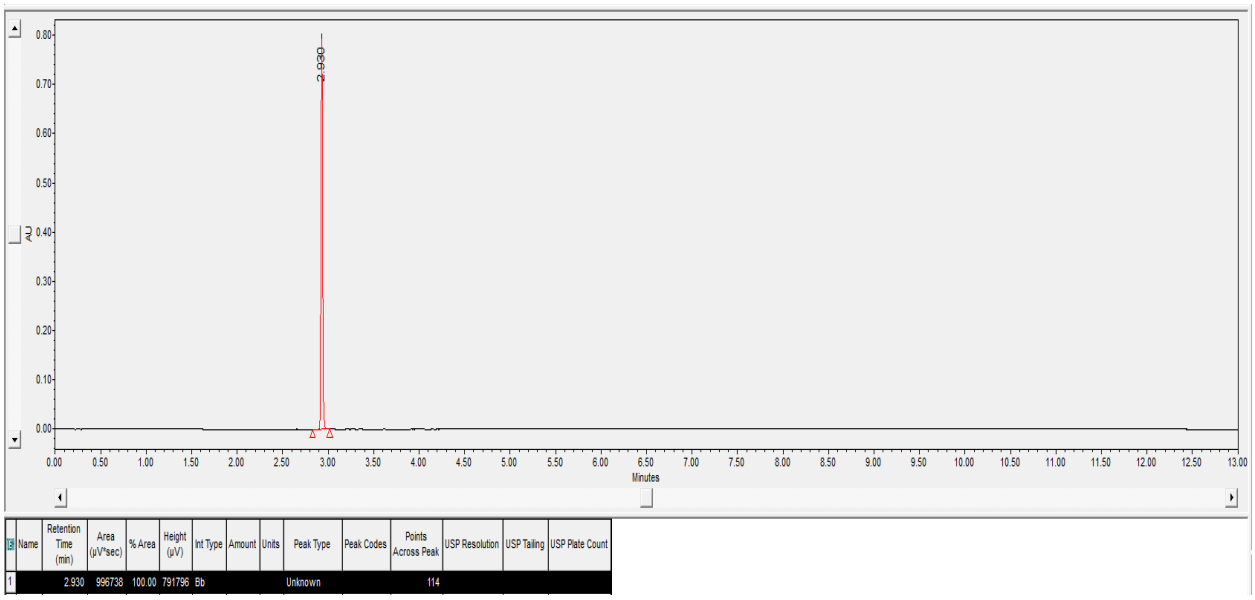


Preparation of CYCLOR (7), Step 1A: To a solution of CAPIC (**2**, 15 g, 105 mmole, 1.0 equiv) in diglyme (75 mL) in a 500 mL 3-neck round-bottom flask fitted with overhead stirrer, thermocouple, and addition funnel was added NaH (7.56g, 189 mmole, 1.8 equiv). The reaction mixture was stirred at room temperature for 30 minutes and gradual evolution of H_2 gas was observed. The temperature of the reaction mixture was slowly increased to 60 °C (10 °C/hr increments). A preheated (55 °C) solution of MeCAN (**5**, 21.19 g, 192.2 mmol, 1.05 equiv) in diglyme (22.5 mL) was added over a period of an hour to the reaction mixture kept at 60 °C. The reaction mixture was allowed to stir at 60 °C for 2 hours.

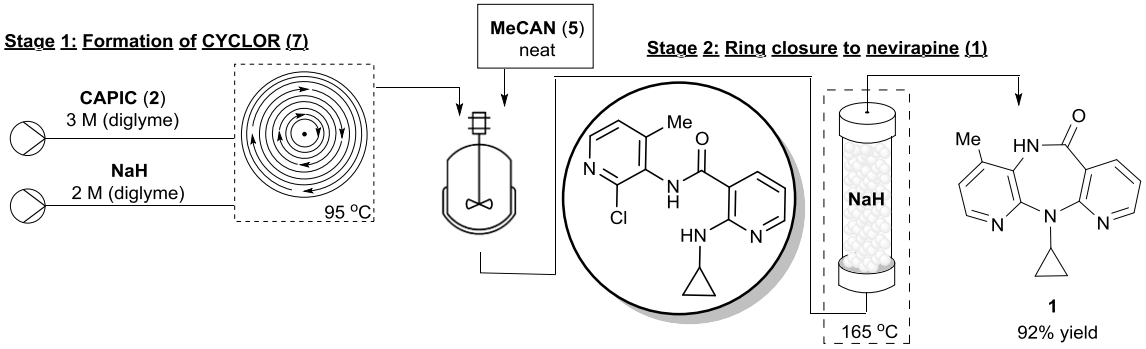
If desired, **7** may be isolated at this stage. The reaction mixture is cooled to 0 – 10 °C and the pH is adjusted to pH 7-8 using glacial acetic acid and stirred for an hour. The precipitate is collected by vacuum filtration and dried under vacuum to a constant weight to afford CYCLOR (**7**) (29.89g, 94%). ^{1}H NMR (300MHz, CHLOROFORM-d) δ = 8.44 (dd, *J* = 1.8, 5.3 Hz, 1 H), 8.21 (d, *J* = 4.7 Hz, 1 H), 8.15 (br. s., 1 H), 7.87 (dd, *J* = 2.1, 7.9 Hz, 1 H), 7.54 (s, 1 H), 7.20 (d, *J* = 5.3 Hz, 1 H), 6.66 (dd, *J* = 4.7, 7.6 Hz, 1 H), 2.95 - 2.84 (m, 1 H), 2.35 (s, 3 H), 0.91 - 0.77 (m, 2 H), 0.62 - 0.47 (m, 2 H). ^{13}C NMR

(75MHz, CHLOROFORM-d) δ = 166.8, 159.2, 153.2, 148.3, 146.9, 136.0, 129.9, 125.1, 111.1, 108.4, 77.4, 76.6, 23.8, 18.8, 7.0. HRMS (ESI) $C_{15}H_{15}ClN_4O$ *m/z* $[M+H]^+$ found 303.0998, expected 303.1012.

Preparation of nevirapine (1), Step 1B: In a 150 mL, 3 neck flask, fitted with overhead stirrer, thermocouple and addition funnel, a suspension of NaH (7.14 g, 178.5 mmol, and 1.7 equiv) in diglyme (22.5 ml) was heated to 105 °C and crude CYCLOR (**7**) reaction mixture from Step 1 (preheated to 80 °C) was added over a period of 30 minutes while maintaining the reaction mixture at 115 °C. The reaction mixture was stirred for 2 hours at 117 °C for ~2 hours then cooled to room temperature. Water (30 mL) was added to quench the excess sodium hydride and the reaction was concentrated in vacuo to remove 60 mL of diglyme. To the resulting suspension was added water (125 mL), cyclohexane (50 mL) and ethanol (15 mL). The pH of the mixture was adjusted to pH 7 using glacial acetic acid (19.5 g, 3.09 mmol) at which precipitate formed. After stirring for 1 hour at 0 °C, the precipitate was collected via vacuum filtration and the filter cake was washed with ethanol: water (1:1 v/v) (2 x 20 mL). The solid was dried between 90-110°C under vacuum to provide nevirapine (25.4 g, 91% over two steps). ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.55 (dd, *J* = 2.0, 4.8 Hz, 1 H), 8.17 (d, *J* = 5.0 Hz, 1 H), 8.13 (dd, *J* = 2.0, 7.8 Hz, 1 H), 7.61 (s, 1 H), 7.08 (dd, *J* = 4.8, 7.8 Hz, 1 H), 6.95 (dd, *J* = 0.6, 4.9 Hz, 1 H), 3.79 (tt, *J* = 3.6, 6.8 Hz, 1 H), 2.37 (s, 3 H), 1.07-0.93 (m, 2 H), 0.59-0.50 (m, 1 H), 0.50-0.41 (m, 1 H). ^{13}C NMR (101MHz, $CDCl_3$) δ = 168.4, 160.5, 153.9, 152.1, 144.3, 140.3, 138.8, 124.8, 121.9, 120.1, 118.9, 29.6, 17.6, 9.1, 8.8. HRMS (ESI) $C_{15}H_{14}N_4O$ *m/z* $[M+H]^+$ found 267.1239, expected 267.1245.



Supplementary Figure 1. Chromatogram showing purity of nevirapine product



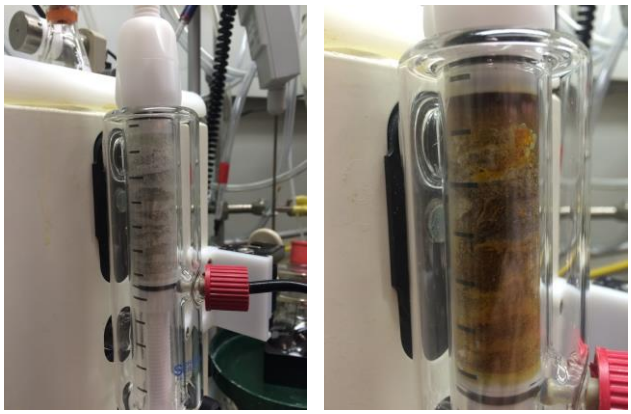
Entry	NaH [equiv]	**5** [equiv]	Combined Flow Rate (mL min^{-1})	Conversion to **7**[a] [%]
1	1.5	1.05	7.22	94
2	1.7	1.10	6.96	98
3	1.6	1.05	7.08	99 (93)[b]
4	1.65	1.0	7.02	98

Entry	Column Temperature (°C)	Flow Rate (mL min^{-1})	Conversion[a] to **1** [%]
5	165	1.0	96 (92[b])
6	140	1.0	60
7	120	1.0	10
8	165	1.5	ND[c]

Supplementary Figure 2. Continuous process diagram and optimization table for the preparation of nevirapine. [a] Conversion determined by HPLC. [b] Isolated yield (wt%). [c] Reactor fouling due to clogging did not allow increased flow rates to be evaluated.

Preparation of NaH packed bed reactor.

To a dry Omnifit column (15 mm x 150 mm), NaH (3 g) and glass beads (Sigma Aldrich, 425-600 µm) were added as alternating thin bands (500 mg of NaH : 1.57 g glass beads per band). Another Kimwipe was packed on top of the beads. A layer of Kimtek wipes and glass beads served as filters at the inlet and outlet of the column. The column was then flushed with anhydrous diglyme via the Vapourtec system



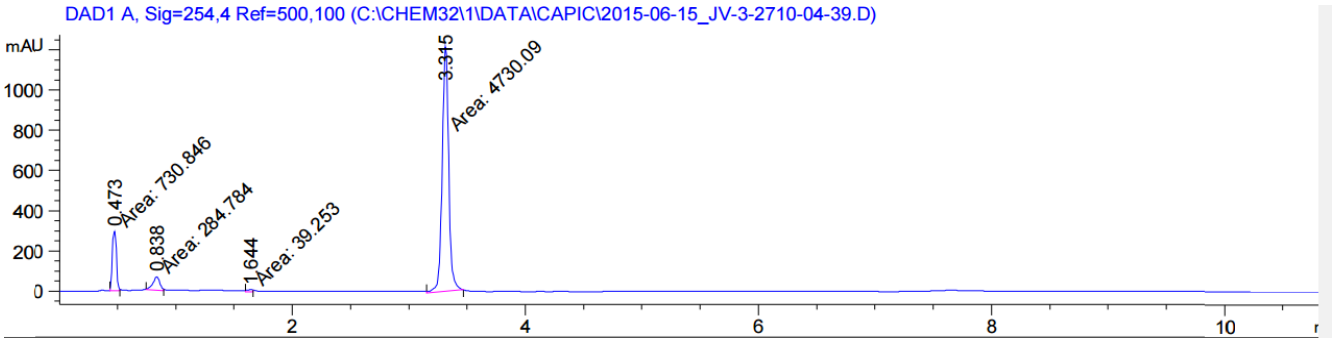
Supplementary Figure 3. (Left) NaH column set up before use (Right) NaH column during reaction.

Procedure for preparation of Nevirapine (1) in flow

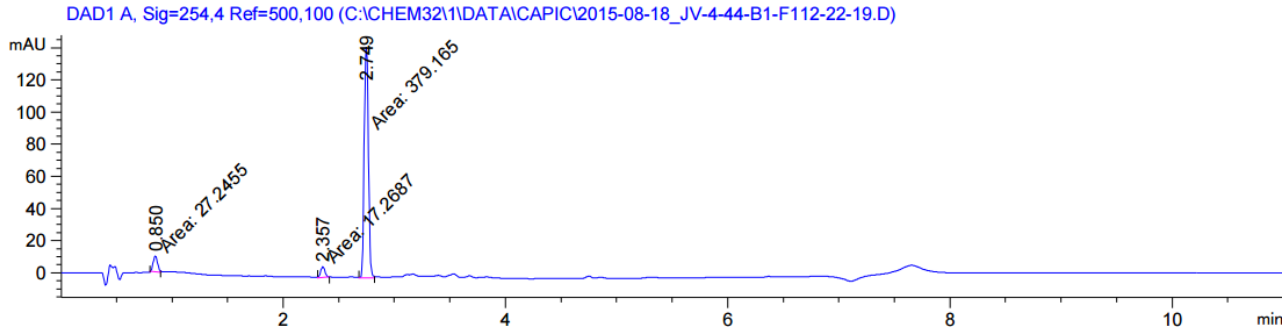
The reactors were assembled according to Supplementary Figure 2 and two reagent stream stocks were prepared: a 3 M solution of CAPIC (**2**) in anhydrous diglyme and, separately, a 2 M slurry of NaH in anhydrous diglyme. CAPIC and and NaH were pumped via an alternating syringe pump (Kloehn) into a spinning disk reactor (Kinetichem Synthetron) heated to 95 °C, at 2.02 mL min^{-1} and 5.00 mL min^{-1}, respectively. One equivalent of the product stream (6.02 mL) was dropped over MeCAN (**5**, 1.0 g, 5.2 mmol, 1.05 eq, neat), stirring in a nitrogen-purged round bottom flask. The reaction mixture was stirred at 65 °C for 2 hours until conversion to 80-85% **7** was observed by high performance liquid chromatography (HPLC) (conversion to 98% by ^{1}HNMR). While the reaction mixture stirred, the NaH column was heated to a temperature of 165 °C. Upon conversion, the stock of **7** was pumped using the E-Series Vapourtec system[3] into the NaH column top-down at 1 mL min^{-1} and the product stream was monitored until a steady-state conversion (~96% by ^{1}HNMR) was observed. The nevirapine product was collected in a flask and purified as in the batch process (92% isolated yield).

Purification of nevirapine.

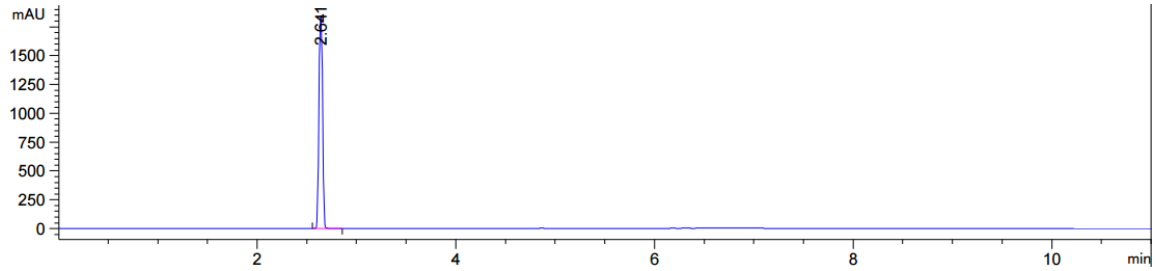
To a cooled (0 °C) suspension of nevirapine (10g, 375.5 mmole) in water (43 ml) was added a 10 M solution of HCl (11.6 ml, 117.5 mmole) dropwise. The solution was allowed to stir for 30 minutes and activated carbon (0.3g) was added. After stirring for 30 minutes, the solution was filtered over Celite. The filtrate was transferred to flask and cooled to 0 °C. A 50% solution of NaOH was added dropwise until a pH of 7 is reached. A white precipitate appeared and the solution was stirred for 30 minutes and filtered. The solid was washed with water (3 x 10ml). The wet cake was dried between 90-110°C under vacuum to a constant weight to provide nevirapine (9.6 g, 96%).



Supplementary Figure 4. Continuous process CYCLOR reaction mixture

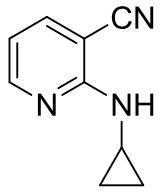


Supplementary Figure 5. Continuous process nevirapine product stream

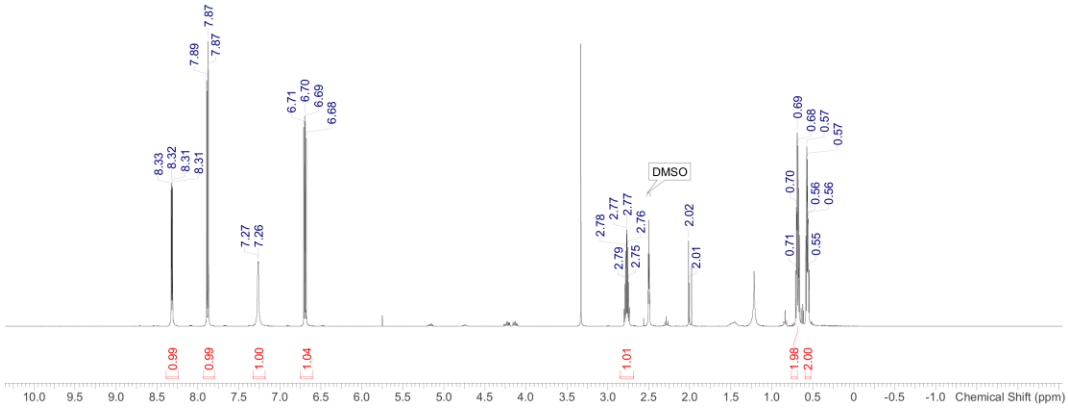


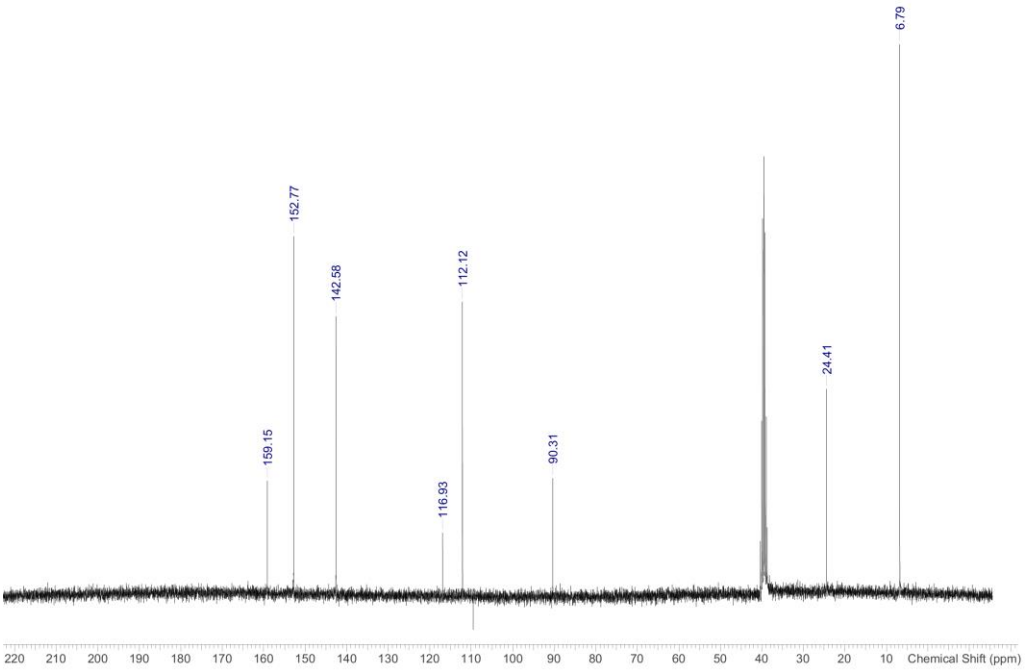
Supplementary Figure 6. Continuous process purified nevirapine

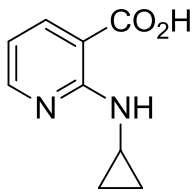
NMR Spectra



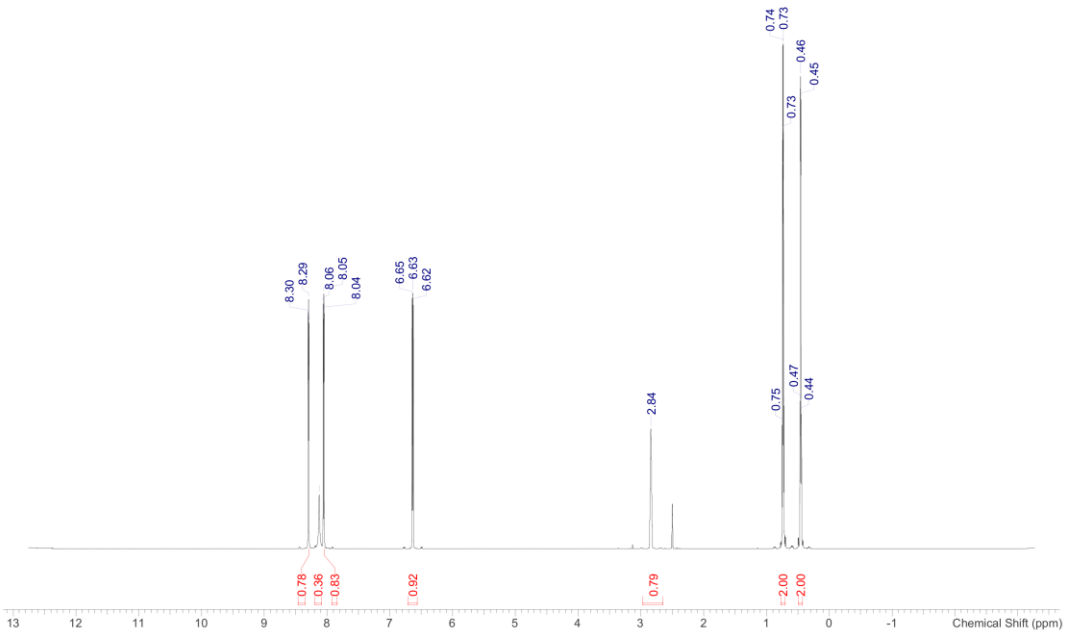
(**8**)

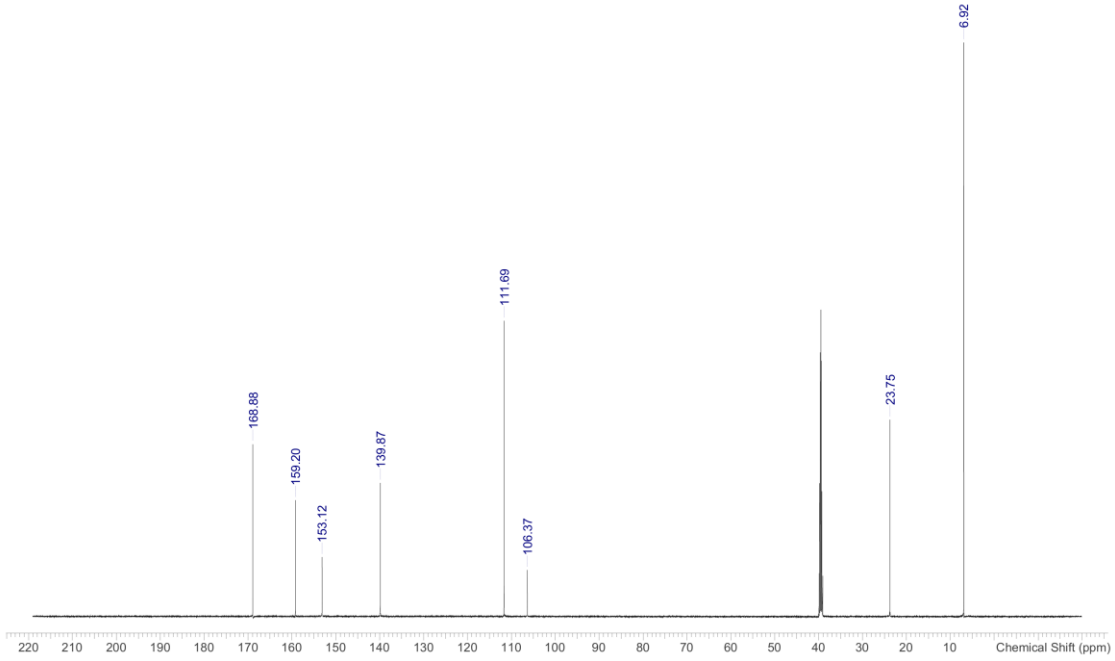


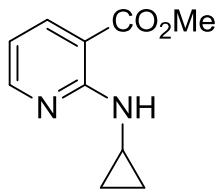



CO2H
N
NH

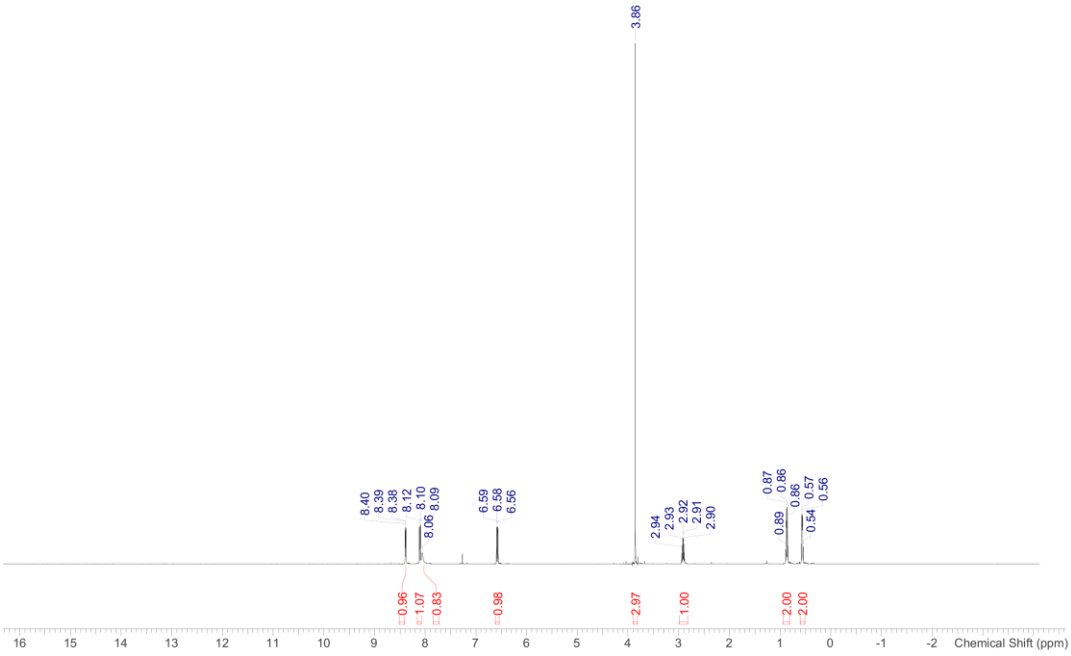
(**4**)

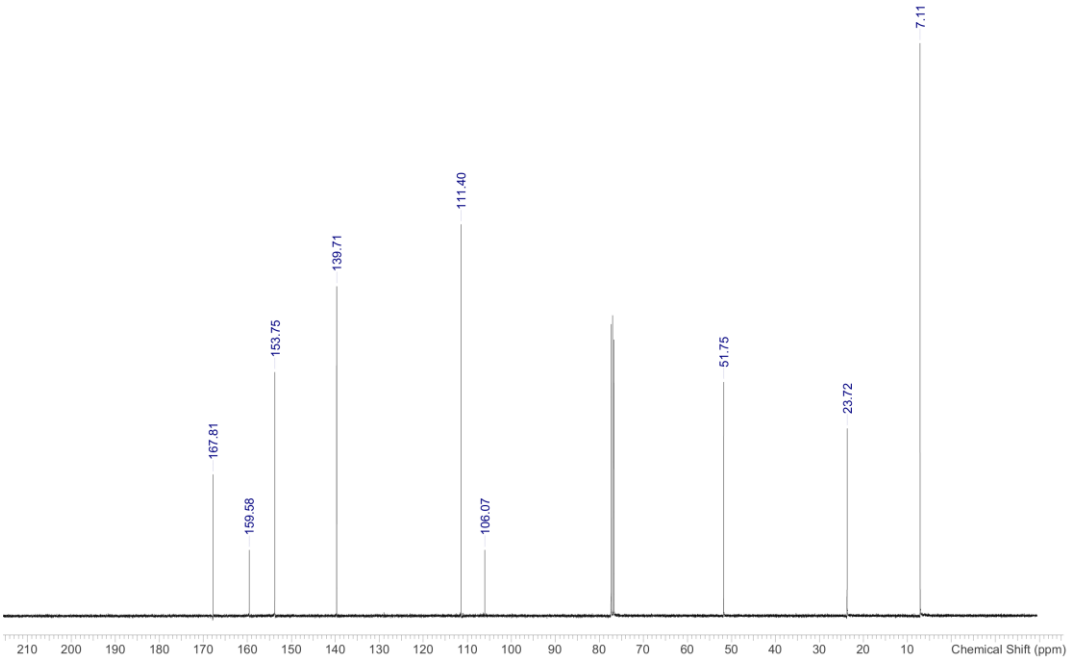

8.30
8.29
8.06
8.05
8.04
6.65
6.63
6.62
2.84
0.74
0.73
0.46
0.45
0.73
0.75
0.47
0.44
0.78
0.36
0.83
0.92
0.79
2.00
2.00
Chemical Shift (ppm)

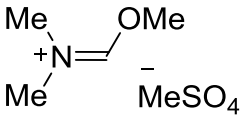

6.92
111.69
168.88
159.20
153.12
139.87
106.37
23.75
Chemical Shift (ppm)


CO2Me
N
NH

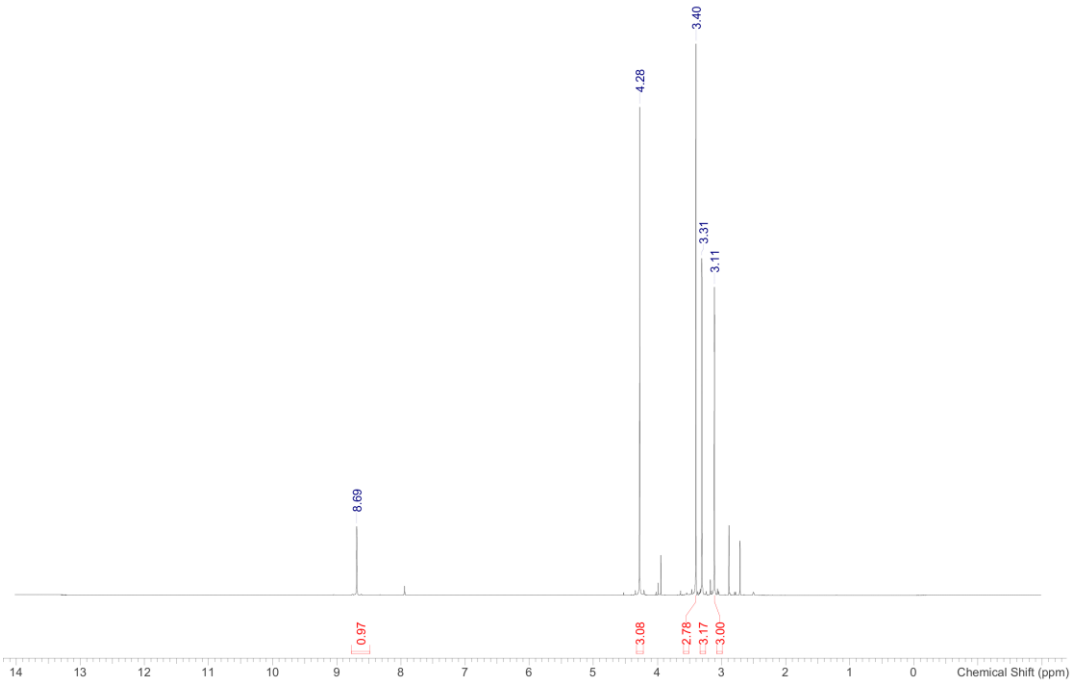
(**5**)

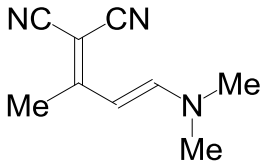

3.86
8.40
8.39
8.38
8.12
8.10
8.09
8.06
6.59
6.58
6.56
2.94
2.93
2.92
2.91
2.90
0.87
0.86
0.89
0.86
0.57
0.54
0.56
0.96
1.07
0.83
0.98
2.97
1.00
2.00
2.00
Chemical Shift (ppm)


7.11
111.40
139.71
153.75
167.81
159.58
106.07
51.75
23.72
Chemical Shift (ppm)

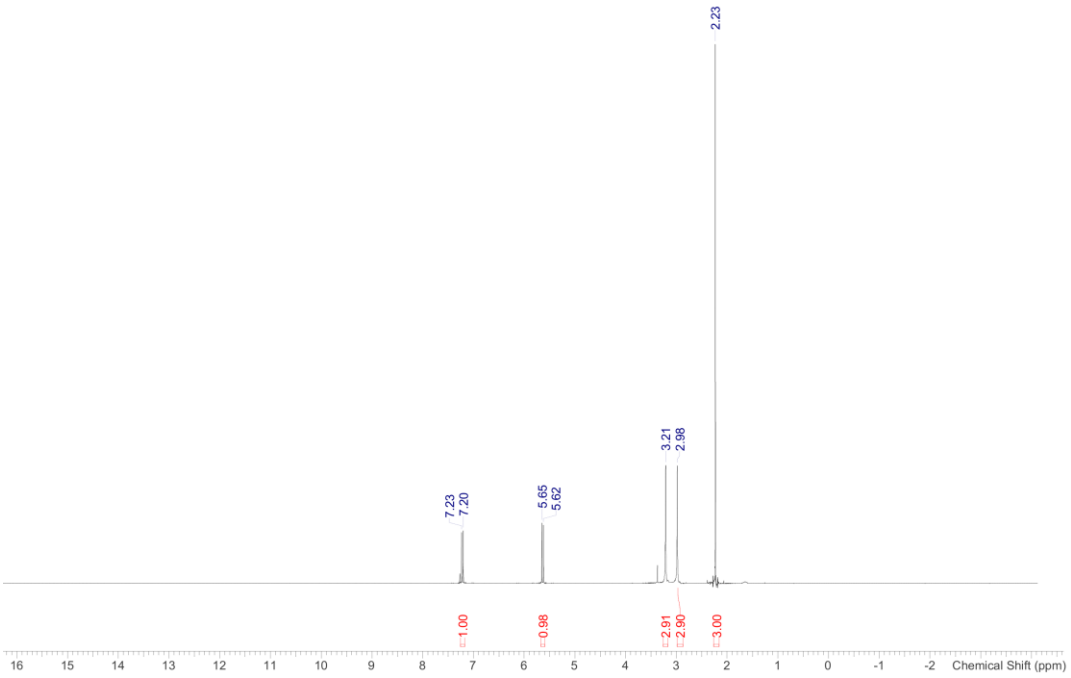

Me
OMe
+N
Me
MeSO4

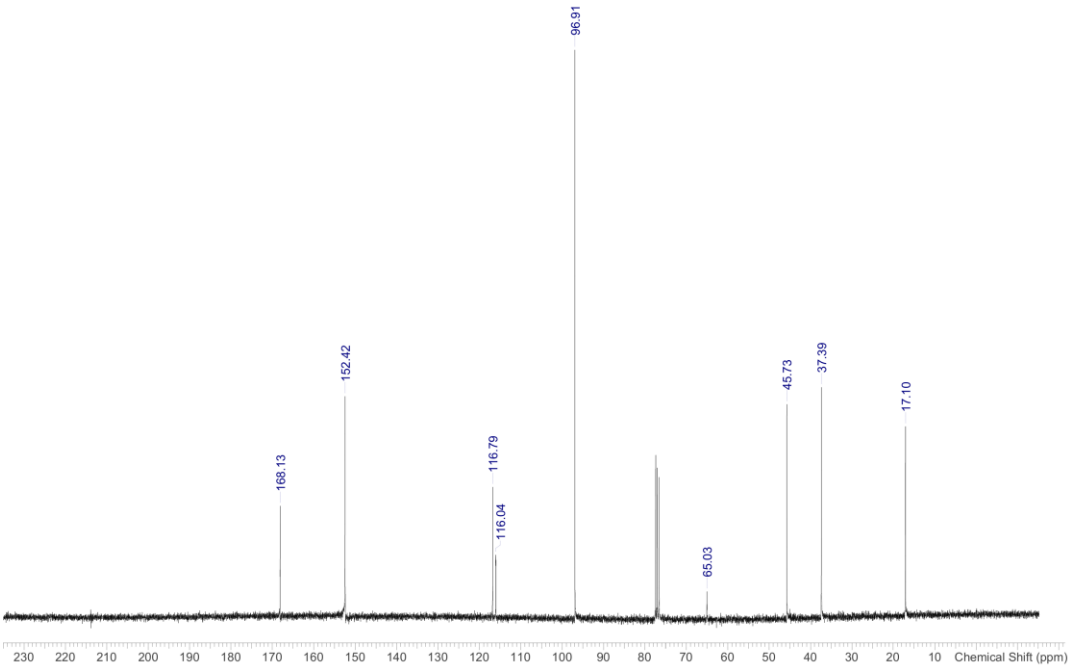
(**14**)

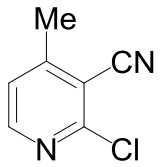

3.40
4.28
3.31
3.11
8.69
0.97
3.08
2.78
3.17
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


NC
CN
Me
N
Me
Me

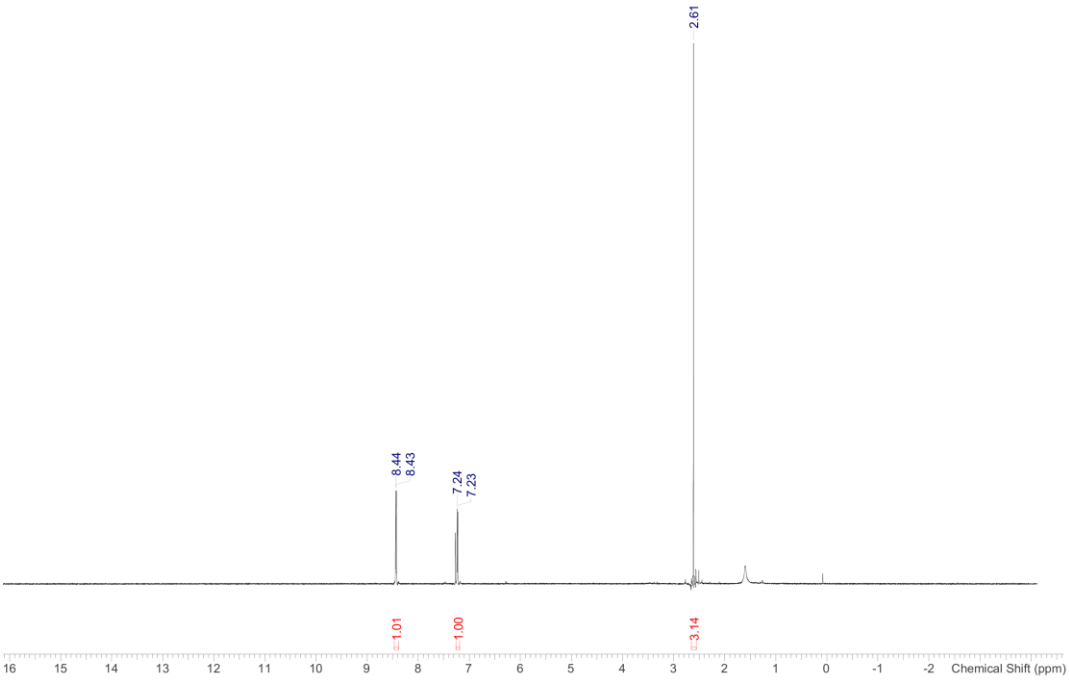
(**11**)


2.23
3.21
2.98
7.23
7.20
5.65
5.62
1.00
0.98
2.91
2.90
3.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 Chemical Shift (ppm)

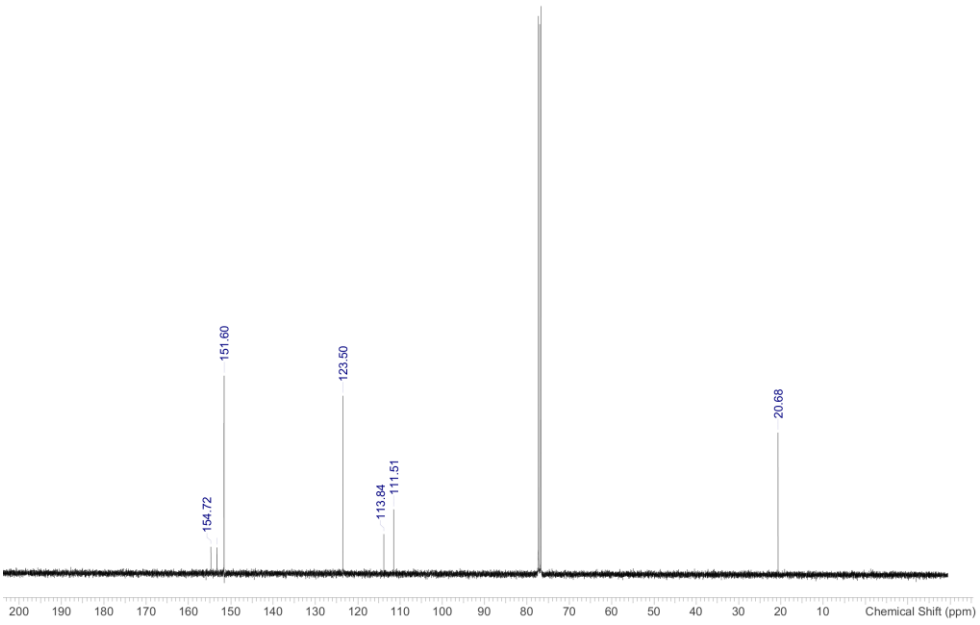

96.91
152.42
168.13
116.79
116.04
65.03
45.73
37.39
17.10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 Chemical Shift (ppm)

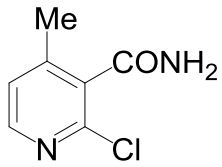

Me
CN
N
Cl

(**12**)

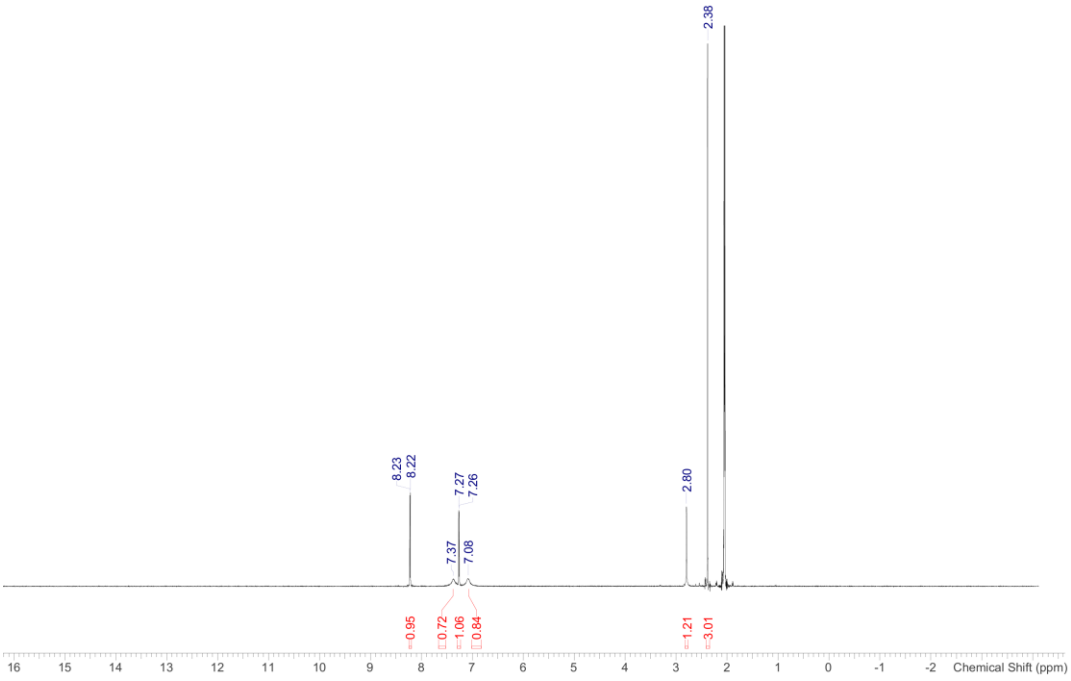

2.61
8.44
8.43
7.24
7.23
1.01
1.00
3.14
Chemical Shift (ppm)

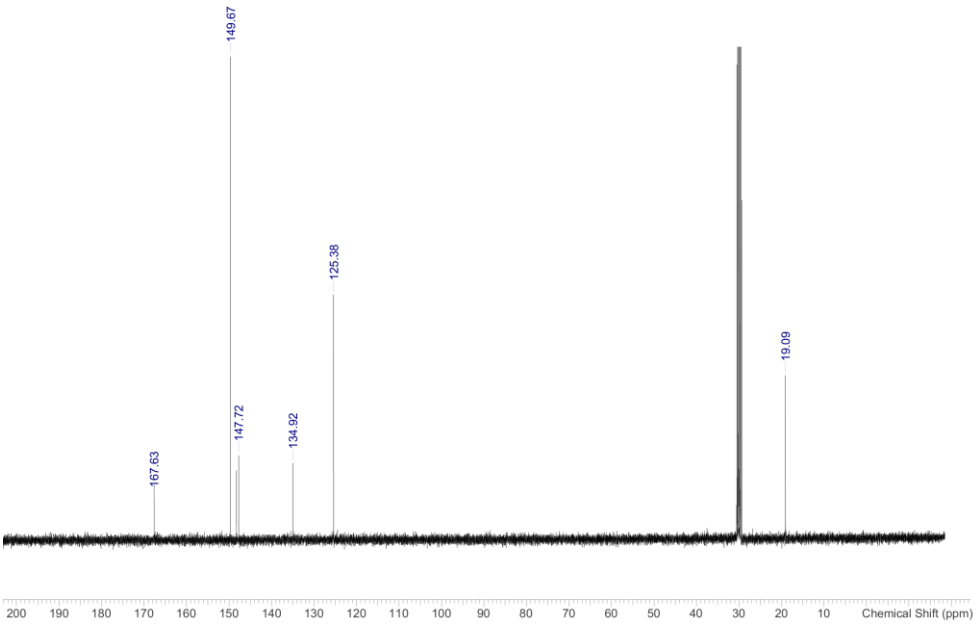
m

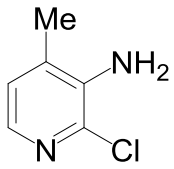

151.60
123.50
20.68
154.72
113.84
111.51
Chemical Shift (ppm)


Me
CONH2
N
Cl

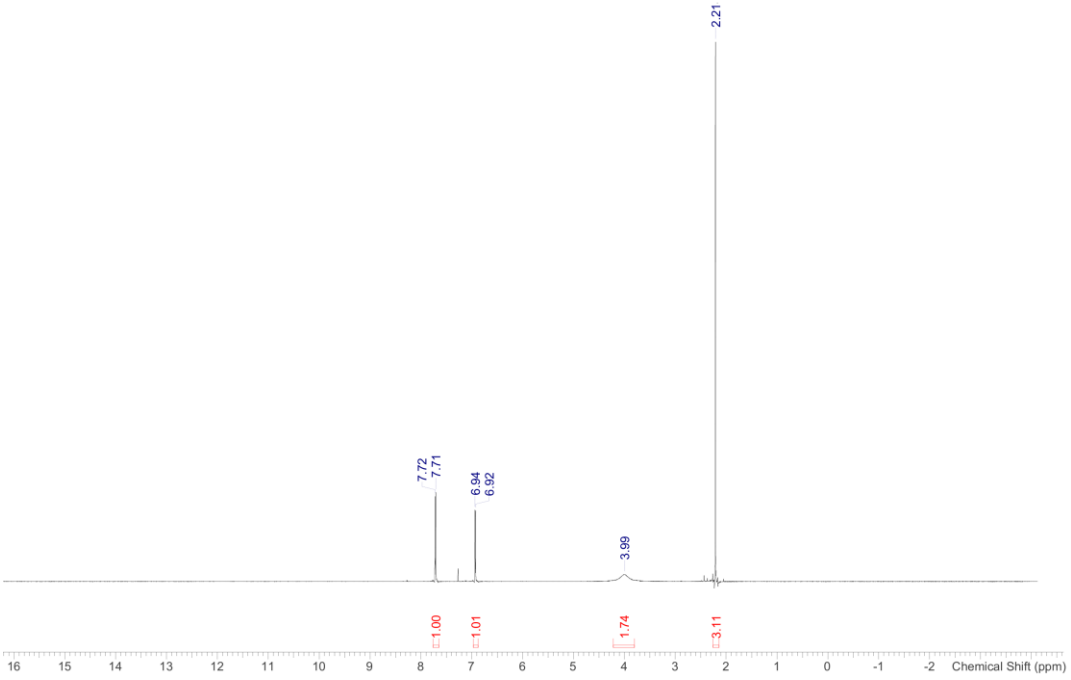
(**15**)

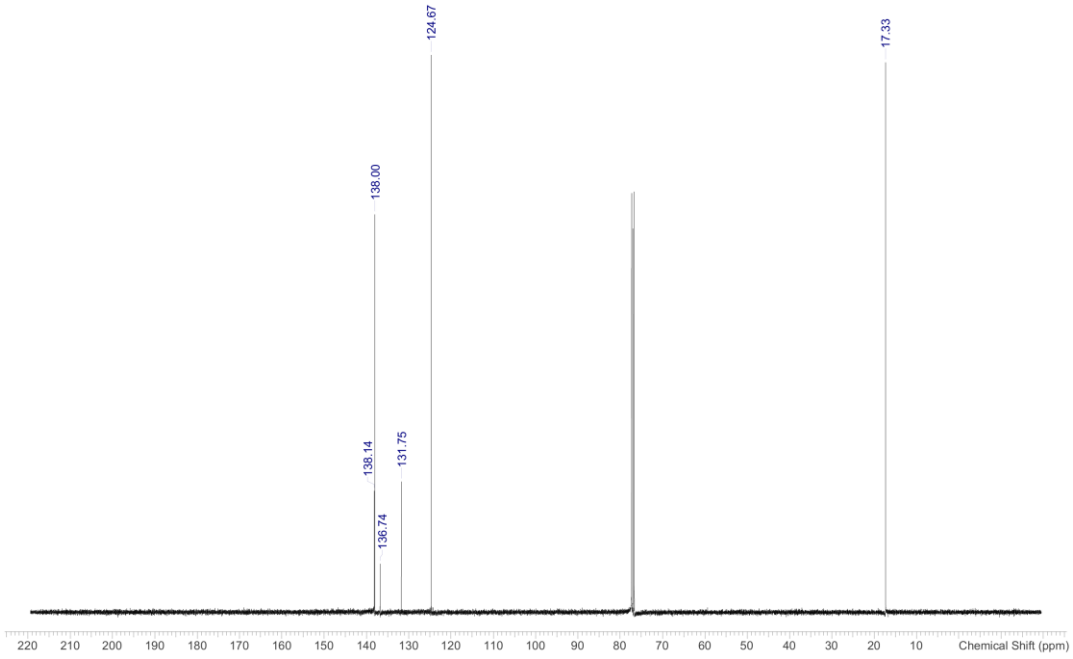

2.38
8.23
8.22
7.27
7.26
2.80
7.37
7.08
0.95
0.72
1.06
0.84
1.21
3.01
Chemical Shift (ppm)

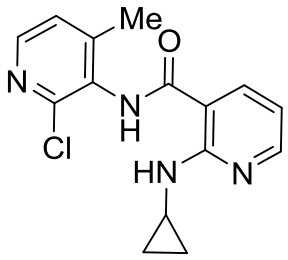

149.67
125.38
19.09
147.72
134.92
167.63
Chemical Shift (ppm)


Me
NH2
N
Cl

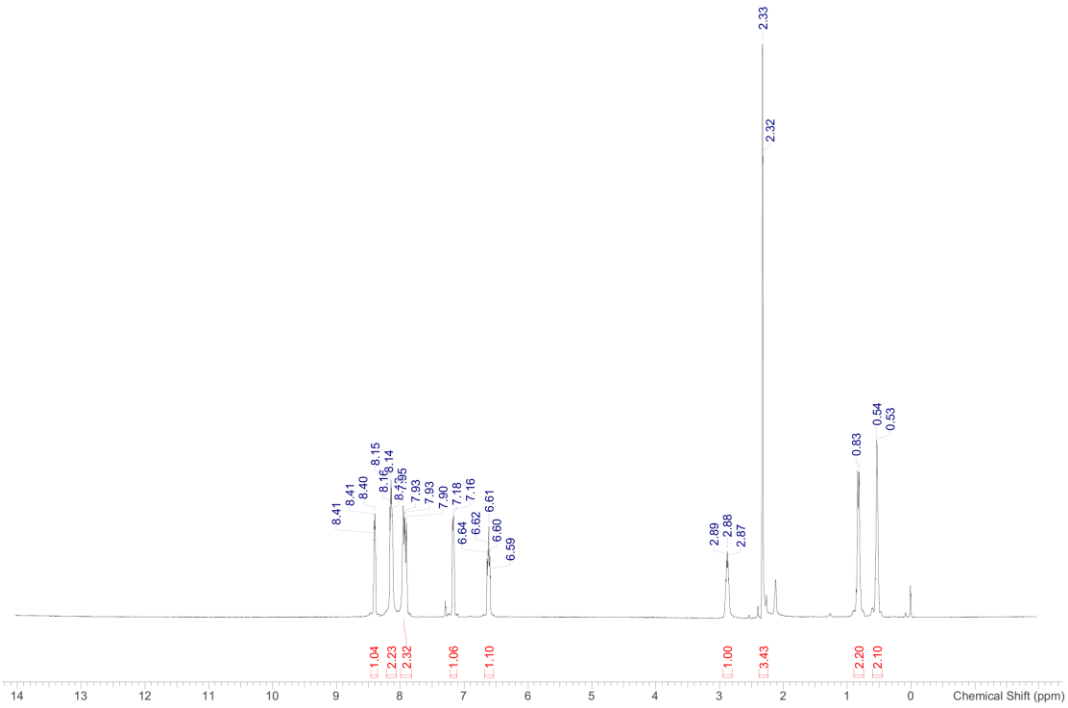
(**2**)

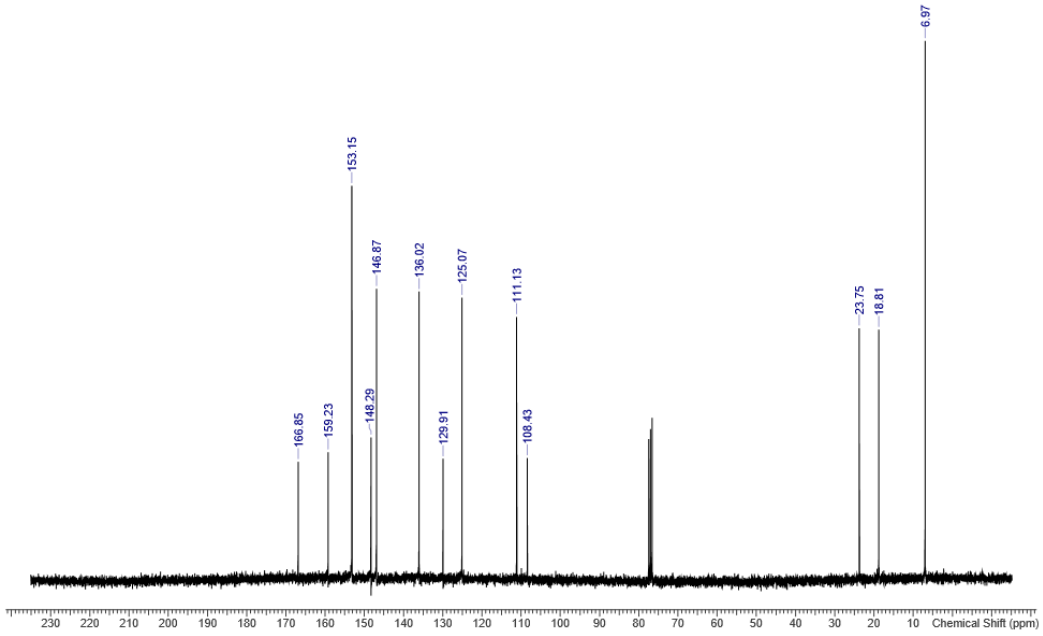

2.21
7.72
7.71
6.94
6.92
3.99
1.00
1.01
1.74
3.11
Chemical Shift (ppm)

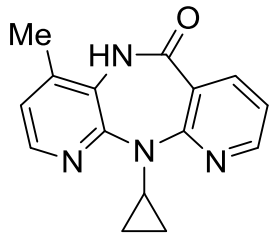

124.67
17.33
138.00
138.14
131.75
136.74
Chemical Shift (ppm)


Me
O
N
N
H
Cl
HN
N

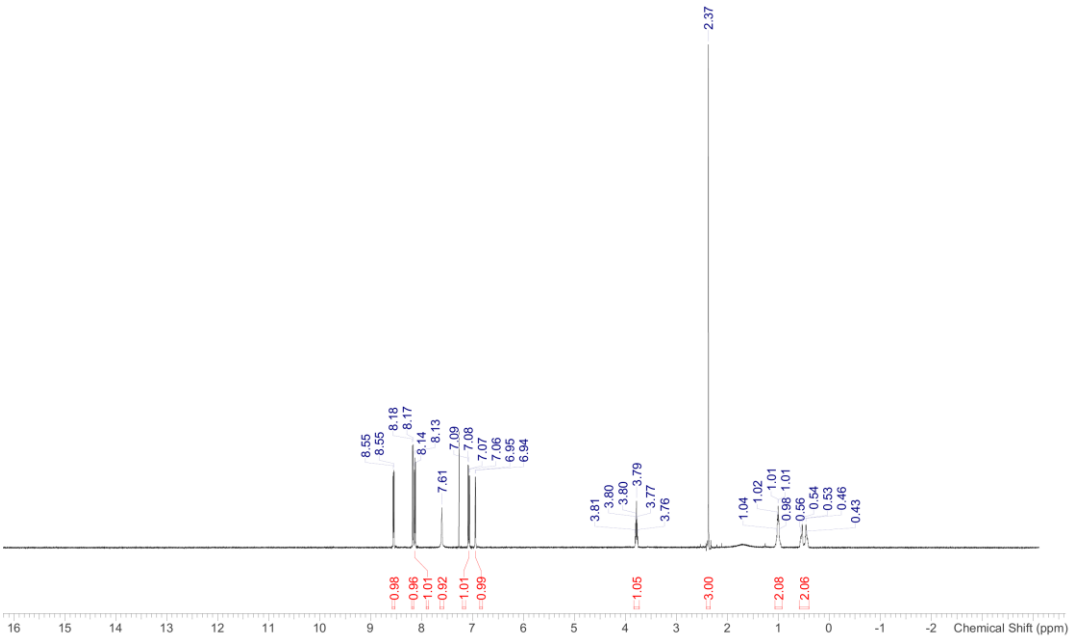
(**7**)

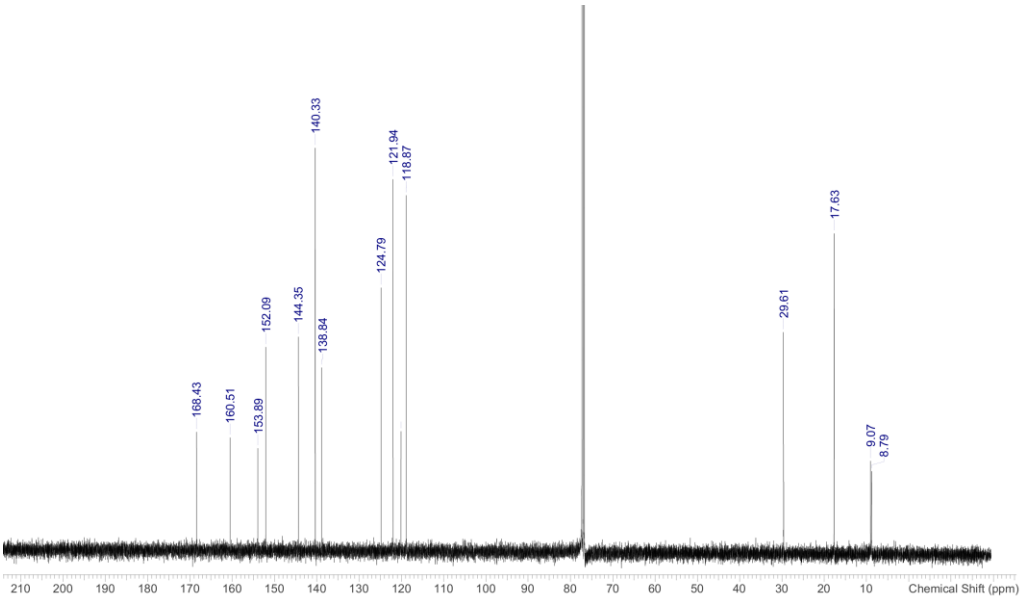

2.33
2.32
0.83
0.54
0.53
8.41
8.41
8.40
8.15
8.14
8.16
8.13
7.95
7.93
7.93
7.90
7.18
7.16
6.64
6.62
6.61
6.60
6.59
2.89
2.88
2.87
1.04
2.23
2.32
1.06
1.10
1.00
3.43
2.20
2.10
Chemical Shift (ppm)


6.97
153.15
146.87
136.02
125.07
111.13
23.75
18.81
166.85
159.23
148.29
129.91
108.43
Chemical Shift (ppm)


Me
HN
O
N
N
N

(**1**)


8.55
8.55
8.18
8.17
8.14
8.13
7.61
7.09
7.08
7.07
7.06
6.95
6.94
3.81
3.80
3.80
3.79
3.77
3.76
2.37
1.04
1.02
1.01
1.01
0.98
0.56
0.54
0.53
0.46
0.43
0.98
0.96
1.01
0.92
1.01
0.99
1.05
3.00
2.08
2.06
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 Chemical Shift (ppm)


168.43
160.51
153.89
152.09
144.35
140.33
138.84
124.79
121.94
118.87
29.61
17.63
9.07
8.79
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 Chemical Shift (ppm)

References

1. Mesnard D, Miginiac L. Synthèse régiospécifique d'amines tertiaires à groupe secondaire bi-insaturé. *Journal of Organometallic Chemistry* 1989, **373**(1)**:** 1-10.

2. Longstreet AR, Campbell BS, Gupton BF, McQuade DT. Improved Synthesis of Mono- and Disubstituted 2-Halonicotinonitriles from Alkylidene Malononitriles. *Org Lett* 2013, **15**(20)**:** 5298-5301.

3. For more information on the Vapourtec E-series please visit: https://www.vapourtec.com/